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| 10/530,088 | 04/01/2005 | Chung K. Chu | G25-080US Nat | 7531 |

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| EXAMINER | |
|---|---|
| OLSON, ERIC | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/530,088 | CHU ET AL. | |
| | Examiner | Art Unit | |
| | Eric S. Olson | 1623 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *02 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-40 and 45-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-40,45-47 and 50* is/are rejected.

7)☒ Claim(s) *48 and 49* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**Detailed Action**

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submissions filed on January 15, 2008 and October 2, 2008 have been entered.

This office action is a response to applicant's communication submitted January 15, 2008 wherein the rejections of record in the previous office action are traversed and Applicant's submission October 2, 2008 wherein new claims 48-50 are introduced. This application is a national stage application of PCT/US03/39029, filed December 8, 2003, which claims benefit of provisional application 60/431812, filed December 9, 2002.

Claims 1-40 and 45-50 are pending in this application.

Claims 1-40 and 45-50 as amended are examined on the merits herein.

Applicant's arguments, submitted October 2, 2008, with respect to the rejection of instant claims 1-4, 8-16, 19-22, 30-34, 37-40, and 45-47 under 35 USC 103(a) as being obvious over Liotta et al. has been fully considered and found to be persuasive to remove the rejection as Applicant has demonstrated unexpected activity of the claimed compounds against a wide range of 3TC or AZT resistant strains of HIV. Therefore the rejection is withdrawn.

Applicant's arguments, submitted October 2, 2008, with respect to the rejection of instant claims 1-22, 30-40, and 45-47 under 35 USC 103(a) as being obvious over Belleau et al. has been fully considered and found to be persuasive to remove the rejection as Applicant has demonstrated unexpected activity of the claimed compounds against a wide range of 3TC or AZT resistant strains of HIV. Therefore the rejection is withdrawn.

Applicant's arguments, submitted October 2, 2008, with respect to the rejection of instant claims 5-7, 17, 18, 23-29, 35, and 36 under 35 USC 103(a) as being obvious over Liotta et al. in view of Merck, has been fully considered and found to be persuasive to remove the rejection as Applicant has demonstrated unexpected activity of the claimed compounds against a wide range of 3TC or AZT resistant strains of HIV. Therefore the rejection is withdrawn.

The following rejections of record in the previous office action are maintained:

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 23-29 and 47 are rejected under 35 U.S.C. 102(e) as being anticipated by Belleau et al. (US patent 7119202, cited in PTO-1449) Belleau et al. discloses a variety of compounds including cis- and trans- 2-acetoxymethyl-4-(thymin-1'-yl) 1,3-dioxolane, and cis- and trans- 2-hydroxymethyl-4-(thymin-1'-yl)-1,3-dioxolane, all of which are compounds of the formula disclosed in instant claim 1. (column 10, lines 59-64) These compounds are useful in therapeutic methods and pharmaceutical compositions for the treatment and prophylaxis of retroviral infections, particularly HIV. (column 11, lines 33-67, column 12, lines 44-67) The compounds may be formulated and administered in combination with other anti-HIV agents of various types, including the reverse transcriptase inhibitors dideoxycytidine and dideoxyinosine. (column 14, lines 28-63) Thus the claimed invention is anticipated by Belleau et al.

Response to Argument: Applicant's arguments, submitted October 2, 2008, with respect to the above ground of rejection have been fully considered but not found to be persuasive to remove the rejection. Applicant argues that Belleau et al. does not disclose the treatment of a drug-resistant form of HIV using the disclosed compounds. However, the rejected claims are drawn to physical compositions of matter, not methods of using said compositions. A compound's usefulness for treating drug-resistant HIV is an inherent property of the claimed composition and does not render these compositions patentable over the prior art. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties Applicant discloses and/or claims are necessarily present. See *In re Spada*, 911 F.2d 705, 709, 15 USPQ 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. As a

result, it is immaterial whether Applicant has discovered novel properties of the claimed composition, since the claims are drawn to a composition which is for all practical purposes the same compound as that disclosed by Belleau et al. Therefore the rejection is deemed proper and maintained.

The following new grounds of rejection are introduced:

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 50 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claim recites, "the method of claim 47" while claim 47 is drawn to a composition. Therefore it is unclear what method is being described, rendering the claim indefinite.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-22, 30-40, and 45-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Belleau et al. (US patent 7119202, cited in PTO-1449) in view of the

Merck Manual of Diagnosis and Therapy, seventeenth edition. (Pp. 1312-1323 of record in previous office action, additionally pp. 1132-1135 included with PTO-892, herein referred to as Merck) further in view of Kim. (Reference included with PTO-892)

The disclosure of Belleau et al. is discussed above. Belleau et al. does not explicitly disclose a method of treating specifically AZT and 3TC resistant strains of HIV or the various strains recited in instant claims 45-47.

Merck discloses that patients with HIV be treated with combination therapy of two or more HIV drugs, including two nucleosides. (p. 1321, left column, paragraph 5 – right column paragraph 4) Merck also discloses that 3TC, ddI, ddC, and abacavir are nucleoside anti-HIV drugs, and additionally that NVP and DLV are non-nucleoside anti-HIV drugs. (p. 1322, table 163-3) Merck also discloses that when changing a failing regimen (i.e. on to which the disease is resistant) two or preferably three new drugs should be started. (p. 1132, right column third paragraph)

Kim et al. discloses the compound dioxolane thymine. (p. 1988 scheme II) This compound is tested against AZT-sensitive and AZT-resistant strains of HIV and seen to be effective against the AZT-resistant strain 9F, with only modest cross-resistance observed. (p. 1992, table IV compound **11**, table V) This stain 9F against which resistance is observed is disclosed to be the same strain G910-6 recited in instant claims 45-47. (p. 1995, right column second paragraph)

It would have been obvious to one of ordinary skill in the art at the time of the invention to practice the methods and compositions of Liotta et al. for treating 3TC or AZT-resistant strains of HIV, for example G910-6.

One of ordinary skill in the art would have been motivated to use the claimed compounds for treating drug resistant cases of HIV because it is routine in the antiviral art to overcome resistance by substituting a new drug regimen, as described by Merck. Furthermore one of ordinary skill in the art would have recognized that the disclosure of Kim et al. demonstrates specific activity against the drug-resistant strain G910-6. One of ordinary skill in the art would reasonably have expected success because this drug is already disclosed to have anti-HIV and anti-G910-6 activity in the prior art. Note that, although claims 1 and 30 were not rejected under 35 USC 103 over Belleau et al. in the first office action, the rejections of dependent claims 2-4 and 31-34 clearly also apply to the base claims as well.

Thus the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's arguments, submitted October 2, 2008, with respect to the above ground of rejection have been fully considered but not found to be persuasive to remove the rejection. Applicant argues that the specification discloses unexpected results for the claimed compounds. However, as discussed above, the prior art already discloses activity of this compound against G910-6. Therefore the claimed method does not produce unexpected results for the full scope of the claimed invention.

Applicant further argues that the Belleau et al. reference was filed nineteen years ago and has not been developed into a clinical therapy, indicating that the prior art did not recognize the potential of dioxolane thymine for treating resistant strains of HIV. Firstly, according to MPEP 2144.05, "[a]bsent a showing of a long-felt need or the

failure of others, the mere passage of time without the claimed invention is not evidence of nonobviousness." *Iron Grip Barbell Co., Inc. v. USA Sports, Inc.,* 392 F.3d at 1324-25, 73 USPQ2d at 1229-30. Therefore the mere fact that Belleau et al. was filed a long time before the instant application does not preclude a finding of obviousness. Furthermore, Kim et al. discloses activity of DOT against an AZT-resistant strain of HIV, thereby indicating that those in the art did in fact recognize that DOT can be used to inhibit AZT-resistant HIV replication.

With respect to the lack of a specific disclosure of drug-resistant HIV in the Belleau et al. reference, it is very common and well-known in the medical and pharmaceutical arts that drug-resistant conditions displaying resistance to one drug should be treated by switching to a different drug. This is the case not only for HIV but for other disorders such as tuberculosis or cancer that display drug-resistant phenotypes. The fact that a particular drug can treat a condition that is resistant to other, structurally distinct drugs is not surprising in the least and would be immediately grasped by anyone of ordinary skill in the art.

With respect to the specific agents 3TC and AZT, applying the therapy of Belleau et al. to these particular drug-resistant strains represents only routine, predictable experimentation. One of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. Putting these embodiments into practice would require only simple *in vitro* experimentation that is utterly routine and well within the level of skill in the art. This modification is the result not of innovation but of ordinary skill and common sense.

Therefore the rejection is deemed proper and maintained.

Claims 1-40 and 45-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liotta et al. (US patent 5852027, cited in PTO-1449) in view of the Merck Manual of Diagnosis and Therapy, seventeenth edition. (Pp. 1312-1323 of record in previous office action, additionally pp. 1132-1135 included with PTO-892, herein referred to as Merck) further in view of Kim. (Reference included with PTO-892)

Liotta et al. discloses methods for prevention and treatment of viral infections, including HIV infections, comprising administering an antiviral 1,3-dioxolane nucleoside, and pharmaceutical compositions comprising such nucleosides. (column 13, line 33 – column 14, line 33) specific pharmaceutically acceptable compounds of the invention of Liotta et al. include compounds identical to those of instant claim 1, including wherein R1 is hydrogen, alkyl, or acyl. Additionally, 2'-deoxy-3'-oxothymidine (R1=H) is shown to inhibit HIV activity *in vitro*. (figure 2, compound 11, also shown TBDMS-protected as compound 6, column 17, lines 33-45) Liotta et al. does not explicitly disclose a method of treating specifically AZT and 3TC resistant strains of HIV. Liotta et al. does not disclose a method or composition additionally comprising a second HIV drug as disclosed in instant claims 5-7, 17, 18, 23-29, 35, and 36.

Merck discloses that patients with HIV be treated with combination therapy of two or more HIV drugs, including two nucleosides. (p. 1321, left column, paragraph 5 – right column paragraph 4) Merck also discloses that 3TC, ddI, ddC, and abacavir are nucleoside anti-HIV drugs, and additionally that NVP and DLV are non-nucleoside anti-

HIV drugs. (p. 1322, table 163-3) Merck also discloses that when changing a failing regimen (i.e. on to which the disease is resistant) two or preferably three new drugs should be started. (p. 1132, right column third paragraph)

Kim et al. discloses the compound dioxolane thymine. (p. 1988 scheme II) This compound is tested against AZT-sensitive and AZT-resistant strains of HIV and seen to be effective against the AZT-resistant strain 9F, with only modest cross-resistance observed. (p. 1992, table IV compound **11**, table V) This stain 9F against which resistance is observed is disclosed to be the same strain G910-6 recited in instant claims 45-47. (p. 1995, right column second paragraph)

It would have been obvious to one of ordinary skill in the art at the time of the invention to practice the methods and compositions of Liotta et al. for treating 3TC or AZT-resistant strains of HIV, for example G910-6, in combination with an additional anti-HIV drug, particularly a second nucleoside such as 3TC, ddI, ddC, or abacavir.

One of ordinary skill in the art would have been motivated to use the claimed compounds for treating drug resistant cases of HIV because it is routine in the antiviral art to overcome resistance by substituting a new drug regimen, as described by Merck. Furthermore one of ordinary skill in the art would have recognized that the disclosure of Kim et al. demonstrates specific activity against the drug-resistant strain G910-6. One of ordinary skill in the art would reasonably have expected success because this drug is already disclosed to have anti-HIV and anti-G910-6 activity in the prior art.

One of ordinary skill in the art at the time of the invention would have been motivated to use an additional anti-HIV drug because Merck discloses that it is standard

practice to administer two nucleosides in combination. One of ordinary skill in the art would have reasonably expected success because both the compounds of Liotta et al. and those disclosed by Merck are seen to be useful for the same purpose, that is the treatment of HIV. It has been held that it is *prima facie* obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose in order to practice a third composition for the very same purpose. The idea of combining them flows logically from their having been taught individually in the prior art. See *In re Kerkhoven*, 205 USPQ 1069, CCPA 1980.

Thus the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's arguments, submitted October 2, 2008, with respect to the above ground of rejection have been fully considered but not found to be persuasive to remove the rejection. Applicant argues that the specification discloses unexpected results for the claimed compounds. However, as discussed above, the prior art already discloses activity of this compound against G910-6. Therefore the claimed method does not produce unexpected results for the full scope of the claimed invention.

Applicant further argues that the Liotta et al. reference was filed seventeen years ago and has not been developed into a clinical therapy, indicating that the prior art did not recognize the potential of dioxolane thymine for treating resistant strains of HIV. Firstly, according to MPEP 2144.05, "[a]bsent a showing of a long-felt need or the failure of others, the mere passage of time without the claimed invention is not evidence of nonobviousness." *Iron Grip Barbell Co., Inc. v. USA Sports, Inc.,* 392 F.3d at 1324-

25, 73 USPQ2d at 1229-30. Therefore the mere fact that Liotta et al. was filed a long time before the instant application does not preclude a finding of obviousness. Furthermore, Kim et al. discloses activity of DOT against an AZT-resistant strain of HIV, thereby indicating that those in the art did in fact recognize that DOT can be used to inhibit AZT-resistant HIV replication.

With respect to the lack of a specific disclosure of drug-resistant HIV in the Liotta et al. reference, it is very common and well-known in the medical and pharmaceutical arts that drug-resistant conditions displaying resistance to one drug should be treated by switching to a different drug. This is the case not only for HIV but for other disorders such as tuberculosis or cancer that display drug-resistant phenotypes. The fact that a particular drug can treat a condition that is resistant to other, structurally distinct drugs is not surprising in the least and would be immediately grasped by anyone of ordinary skill in the art.

With respect to the specific agents 3TC and AZT, applying the therapy of Liotta et al. to these particular drug-resistant strains represents only routine, predictable experimentation. One of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. Putting these embodiments into practice would require only simple *in vitro* experimentation that is utterly routine and well within the level of skill in the art. This modification is the result not of innovation but of ordinary skill and common sense.

Therefore the rejection is deemed proper and maintained.

**Conclusion**

Claims 1-40, 45-47, and 50 are rejected. Claims 48 and 49 are objected to for depending from a rejected base claim but would be allowable if rewritten in independent form incorporating all the limitations of the rejected base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Eric S Olson/
Examiner, Art Unit 1623
10/27/2008

/Shaojia Anna Jiang/
Supervisory Patent Examiner, Art Unit 1623